section, if alternative elements are positively recited in the specification, they may be explicitly excluded in the claims. In the present factual situation, as indicated above, "an acrylic adhesive" is positively recited in the specification (page 5, line 6). Therefore, according to the MPEP, it may be explicitly excluded in the claims.

Stated another way, according to the description of the present specification, at least two kinds of patches are disclosed, one a patch consisting of the adhesive including an acrylic adhesive, and the other a patch consisting of the adhesive not including an acrylic adhesive. These two patches are clearly and separately indicated therein. The amendment to claim 1 merely excludes the patch containing an acrylic adhesive.

In view of these considerations, Applicants take the position that the presently claimed invention as set forth in claim 1 is clearly supported by the specification, and accordingly, the rejection of the claims under the first paragraph of 35 U.S.C. §112 should be withdrawn.

The patentability of the presently claimed invention over the disclosures of the references relied upon by the Examiner in rejecting the claims will be apparent upon consideration of the following remarks.

Thus, the rejection of claims 1-4 under 35 U.S.C. §103(a) as being unpatentable over Hoffmann et al. in view of Higo et al. and further in view of Stroppolo et al. is respectfully traversed.

Present Invention

The present invention relates to a patch containing tulobuterol, prepared by laminating an adhesive layer consisting of a rubber, a non-acrylic adhesive resin (such as petroleum resin, polyterpene resin, polyolein resin and saturated alicyclic hydrocarbon resin as recited in claim 4), and a plasticizer on a backing, wherein 1 to 4 w/w % of tulobuterol as an active ingredient and 0.1 to 3 w/w % of a higher fatty acid (such as a C_{11-22} fatty acid as recited in claim 3), as a drug release controlling agent are contained in the adhesive layer.

The patch of the present invention is characterized by containing tulobuterol in such a low concentration as 1 to 4 w/w % as well as a higher fatty acid such as a C_{11-22} fatty acid as a drug release controlling agent. This patch exhibits enough drug releasing amount with controllability of stable drug-release despite the fact that tulobuterol is contained in a low concentration.

(1) Comparison with U.S. Patent 5,254,348 (Hoffmann et al.)

This patent relates to a preparation for asthma therapy containing tulobuterol as an active ingredient, more in detail, a transdermal therapeutic system with tulobuterol or one of the pharmaceutically acceptable salts thereof as active substance, comprising a backing layer which is substantially impermeable to the active substance and at least one matrix layer which comprises at least one styrene-1,3-diene block copolymer.

The object of Hoffmann et al.'s invention is to provide a transdermal therapeutic system with tulobuterol suitable for asthma therapy, and this object is achieved by a transdermal therapeutic system comprising as active substance tulobuterol in a matrix containing at least one polystyrene-l,3- diene-polystyrene block copolymer (column 2, lines 46-53).

The point of Hoffmann et al.'s invention is only to use **polystyrene-1,3-diene-polystyrene block copolymer in a matrix** comprising as active substance tulobuterol in a transdermal therapeutic system suitable for asthma therapy, and not anything else.

As examples of solubilizers and plasticizers, various kinds of substances such as fatty acids, mineral oil, glycerol, paraffins and so on are only indicated in this patent (column 3, lines 58 to 65). However, a description of the fatty acids is not found in any part other than the above description. In addition, although the term "mineral oil" is described therein, this term does not include any fatty acid, as shown in the attached Appendix A (page 1241 from The Merck Index). Therefore, the Examiner's statement "**mineral oil** (reading on the higher fatty acid and C_{11-22} fatty acid of claims 1 and 3)" in the Office Action at page 4, lines 8-9 should be withdrawn. In this patent, although rubber, adhesive resin, and plasticizer are described as indicated by the Examiner, it can not be even speculated from this patent that higher fatty acids, especially C_{11-22} fatty acids are used as a release controlling agent for tulobuterol.

Therefore, the subject matter of the presently claimed invention and the subject matter disclosed in this patent are completely different in technical concept or idea.

(2) Comparison with U.S. Patent 5,866,157 (Higo et al.)

The object of Higo et al.'s invention is to provide a matrix type patch formulation which increases percutaneous absorbability of a physiological active substance and is extremely reduced in irritation to the skin where the formulation is applied (abstract, column 2, lines 31-44).

Higo et al.'s invention is characterized by increasing percuteneous permeability of a physiological active substance such as tulobuterol by formulating an organic acid and an absorption enhancer in to the adhesive layer. The object of Higo et al.'s invention is attained only by using a combination of an organic acid and an absorption enhancer.

A higher fatty acid such as C_{11-20} fatty acid is illustrated as one of various absorption enhancers of a physiological active substance therein, but this acid is not used alone in any working examples thereof.

As mentioned above, the present invention is clearly different from Higo et al. in the problem to be solved and the means for solving the problem. Therefore, a skilled person in the art would not be led to use, instead of a combination of an organic acid and an absorption enhancer described in Higo et al., a higher fatty acid such as a C_{11-22} fatty acid alone, to prepare a patch containing tulobuterol in a lower concentration and having a stable release controllability.

Furthermore, Higo et al. would not motivate the art-skilled to use a C_{11-22} fatty acid with the expectation of obtaining an improved patch preparation containing tulobuterol.

(3) Comparison with U.S. Patent 5,312,627 (Stroppolo et al.)

This patent relates to a transdermal therapeutic system in a polymer matrix based on polyisobutylene suitable for the administration of bronchodilator drugs, namely a transdermal therapeutic system in a polymer matrix for the administration of bronchodilator drugs, the system consisting of a bronchodilator drug in solid form and a matrix in which the substance is suspended. The matrix comprises **a mixture of medium molecular weight polyisobutylene** (10-60% by weight) and **high molecular weight polyisobutylene** (9-25% by weight) in a ratio between 1 and 2.3 (claim 1 for example).

Stroppolo et al.'s invention was completed by finding that bronchodilator drugs can be administered by a transdermal route by employing a system in a polymer matrix constituted by a mixture of high and medium molecular weight polyisobutylene, thus obtaining a slow and prolonged release of the active ingredient, particularly effective in the treatment of bronchial asthma (column 3, lines 37-43). The polymer matrix used in this patent is characterized by the sole presence of a mixture of medium molecular weight polyisobutylene and high molecular weight polyisobutylene mixed in a weight ratio between 1 and 2.3 (column 4, lines 57-61).

On the other hand, the present invention does not need high and medium molecular weight polyisobutylenes. Therefore, the present invention is different from Stroppolo et al.'s invention in terms of constitution.

This patent describes that "The polyisobutylene polymer matrix contains the drug in a dispersed form in amounts preferably comprised between 10% and 50% by weight" (column 3, lines 61-67). According to this description, it is apparent that the system is not intended to contain tulobuterol in a concentration of 1 to 4 % w/w to control the release with a drug release controlling agent.

On the other hand, the patch of the present invention is characterized by containing tulobuterol in such a low concentration as 1 to 4 w/w % and a higher fatty acid such as a C_{11-22} fatty acid as a drug release controlling agent, and the patch exhibits enough drug releasing amount and has controllability of a stable drug-release despite the fact that tulobuterol is contained in such a low concentration. Therefore, the present invention is completely different from Stroppolo et al.'s invention in term of constitution.

(4) Rejection under 35 U.S.C. §103 as being unpatentable over Hoffmann et al. in view of Higo et al. and Stroppolo et al.

As explained above, the subject matter of the present invention is completely different from Hoffmann et al.'s invention in the point of using a higher fatty acid as a release controlling agent for tulobuterol. Further, the subject matter of the present invention is different from Higo et al. in the point of excluding a combination of an organic acid and an absorption enhancer, and is also different from Stroppolo et al. in the above-mentioned points.

A skilled person in the art would not be motivated to combine Hoffmann et al., Stroppolo et al. and Higo et al., and even if these references were combined, it would not lead a skilled person in the art to combine 1 to 4 w/w % of tulobuterol, a rubber, a non-acrylic adhesive resin, a higher fatty acid, and a plasticizer into a patch formulation, nor would the art-skilled expect the excellent effect of controllability of stable drug-release of the present invention.

For these reasons, Applicants take the position that the presently claimed invention is clearly patentable over the applied references.

Therefore, in view of the foregoing remarks, it is submitted that each of the grounds of rejection set forth by the Examiner has been overcome, and that the application is in condition for allowance. Such allowance is solicited.

Respectfully submitted,

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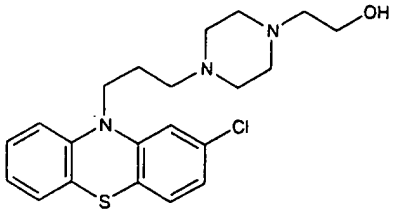


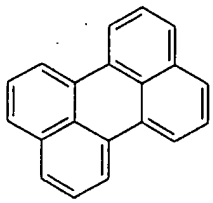
Crystals. Sensitive to light. mp 94-100°. $bp_{0.15}$ 214-218°; bp_1 278-281°. Practically insol in water. Soly (mg/ml): ethanol 153; acetone 82. Practically insol in sesame oil.

Dihydrochloride. $C_{21}H_{28}Cl_3N_3OS$. Crystals from alcohol. mp 225-226°.

THERAP CAT: Antipsychotic.

THERAP CAT (VET): Tranquilizer, pre-anesthetic agent.

7184. Perylene. [198-55-0] Dibenz[*de,kl*]anthracene; *peri*-dinaphthalene. $C_{20}H_{12}$; mol wt 252.31. C 95.21%, H 4.79%. Occurs in coal tar. Isoln from pitch distillate: Cook *et al., J. Chem. Soc.* **1933**, 395. From 2,2'-dihydroxy-1,1'-dinaphthyl: Zinke *et al., Monatsh. Chem.* **64**, 415 (1934). From the reaction of phenanthrene with acrolein in anhydr HF: Weinmayr, US **2145905** (1939); *cf. J. Am. Chem. Soc.* **61**, 949 (1939).



Yellow to colorless crystals from toluene. mp 273-274°. Sublimes 350-400°. d 1.35. Absorption spectrum: Clar, *Ber.* **65**, 848 (1932). Freely sol in CS_2, chloroform; moderately sol in benzene; slightly in ether, alcohol, acetone; very sparingly sol in petr ether. Insol in water.

Monopicrate. $C_{26}H_{15}N_3O_7$. Dark violet-blue needles, mp 223-225°.

7185. Petrolatum. Petroleum jelly; paraffin jelly; vaseline. Purified mixture of semisolid hydrocarbons, chiefly of the methane series of the general formula C_nH_{2n+2}. Actually, petrolatum is a colloidal system of nonstraight-chain solid hydrocarbons and high-boiling liq hydrocarbons, in which most of the liq hydrocarbons are held inside the micelles. Detailed historical account including chemistry and modern mfg methods: Schindler, *Drug Cosmet. Ind.* **89**, 36-37, 76, 78-80, 82 (1961).

Yellowish to light amber or white, semisolid, unctuous mass; practically odorless and tasteless. d_{25}^{60} 0.820-0.865. mp 38-54°. n_D^{60} 1.460-1.474. White petrolatum is transparent in thin layers even at 0°. Practically insol in water, glycerol, alcohol. Sol in benzene, chloroform, ether, petr ether, carbon disulfide, oils.

USE: As ointment base in pharmaceuticals and cosmetics. Lubricating firearms and machinery, leather grease, shoe polish, rust preventives, modeling clays.

7186. Petrolatum, Liquid. Liquid paraffin; mineral oil; white mineral oil; paraffin oil; Clearteck; Drakeol; Hevyteck; Kremol; Kaydol; Alboline; Nujol; Paroleine; Saxol; Adepsine oil; Glymol. A mixture of liquid hydrocarbons from petroleum.

Colorless, oily liquid; practically tasteless and odorless even when warmed. The density of the "light" oil is usually 0.83-0.860; the "heavy" 0.875-0.905. Surface tension at 25° slightly below 35 dynes/cm. Insol in water, alc. Sol in benzene, chloroform, ether, carbon disulfide, petr ether, oils.

USE: Lubricant. Pharmaceutic aid (vehicle, solvent). As formulation aid in foods. In cosmetics as emollient.

THERAP CAT: Cathartic.

THERAP CAT (VET): Laxative, externally as a protectant, lubricant.

7187. Petroleum. Crude oil; mineral oil; rock oil; coal oil; seneca oil. Consists of a mixture of hydrocarbons from C_2H_6 and up—chiefly of the paraffins, cycloparaffins, or of cyclic aromatic hydrocarbons, with small amounts of benzene hydrocarbons, sulfur, and oxygenated compounds. *Occurrence:* U.S., Mexico, Iran, Russia, Roumania, Poland, Dutch East Indies, etc.

Dark yellow to brown or greenish-black, oily liquid. Insol in water and only a small portion of it may dissolve in alcohol; sol in benzene, chloroform, ether.

USE: Source of gasoline, petr ether, liq and solid petrolatum, fuel and lubricating oils, butane, isopropyl alcohol, etc.

7188. Petroleum Benzin. [8030-30-6] Naphtha; benzin; petroleum naphtha. Term that has been applied to low boiling fractions of petroleum, consisting chiefly of hydrocarbons of the methane series, principally pentanes and hexanes.

Clear, colorless, nonfluorescent, *highly flammable*, volatile liq; characteristic odor; does not solidify in the cold. The vapors mixed with air explode if ignited. *Keep tightly closed in a cool place and away from fire.* d 0.625-0.660; bp between 35-80°. Insol in water. Miscible with abs alc, benzene, chloroform, ether, carbon disulfide, carbon tetrachloride, and oils except castor oil.

Caution: Potential symptoms of overexposure are lightheadedness, drowsiness; irritation of eyes, nose and skin; dermatitis. *See NIOSH Pocket Guide to Chemical Hazards* (DHHS/NIOSH 97-140, 1997) p 220.

USE: Pharmaceutic aid (solvent).

THERAP CAT: Counterirritant.

7189. Petroselinic Acid. [593-39-5] *cis*-6-Octadecenoic acid; petroselic acid; 5-heptadecylene-1-carboxylic acid; Δ^5-octadecylenic acid. $C_{18}H_{34}O_2$; mol wt 282.46. C 76.54%, H 12.13%, O 11.33%. $CH_3(CH_2)_{10}CH{=}CH(CH_2)_4COOH$. Isoln from parsley seed oil, the oil extracted from dried ripe seed of *Petroselinum hortense* Hoffm., *Umbelliferae:* Fore *et al., J. Am. Oil Chem. Soc.* **37**, 490 (1960).

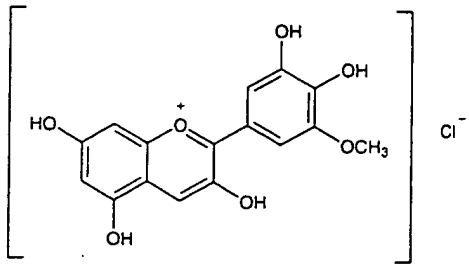
Leaflets from petr ether, mp 29.5-30.1°. bp_{18} 237-238°; d_4^{40} 0.8700. n_D^{40} 1.4533. Low temp solubilities: Heptane at −10° = 0.50 g/100 g solution; methanol at −20° = 0.48 g/100 g; ethyl acetate at −20° = 0.73 g/100 g; ether at −20° = 3.52 g/100 g. Ozonolysis yields 85% of adipic acid. Neutralization equivalent: 282.45; iodine value 89.87%.

Methyl ester. $C_{19}H_{36}O_2$. Liq, d_4^{20} 0.8767; n_D^{20} 1.4501; bp_{10} 208-210°.

Glyceryl triester. Glyceryl tripetroselinate; tripetroselin. $C_{57}H_{104}O_6$. Solidifies at 16.5°. n_D^{40} 1.4619.

Amide. $C_{18}H_{35}NO$. Needles, mp 76°.

7190. Petunidin. [1429-30-7] 2-(3,4-Dihydroxy-5-methoxyphenyl)-3,5,7-trihydroxy-1-benzopyrylium chloride; 3,3',4',5,7-pentahydroxy-5'-methoxyflavylium chloride; petunidol. $C_{16}H_{13}ClO_7$; mol wt 352.72. C 54.48%, H 3.71%, Cl 10.05%, O 31.75%. The aglucone of petunin: Willstätter, Burdick, *Ann.* **412**, 217 (1917). Synthesis: Bradley *et al., J. Chem. Soc.* **1930**, 793; Robinson, Robinson, *Biochem. J.* **25**, 1687 (1931). Chromatographic separation: Spaeth, Rosenblatt, *Anal. Chem.* **22**, 1321 (1950).



Gray-brown leaflets or prisms from dil HCl.

3,5-Diglucoside. [25846-73-5] 2-(3,4-Dihydroxy-5-methoxyphenyl)-3,5-bis(β-D-glucopyranosyloxy)-7-hydroxy-1-benzopyrylium chloride; petunin. $C_{28}H_{33}ClO_{17}$; mol wt 677.00. From *Petunia hybrida* Hort., *Solanaceae:* Willstätter, Burdick, *loc. cit.* Synthesis: Bell, Robinson, *J. Chem. Soc.* **1934**, 1604. Violet plates with a coppery luster from dil HCl, mp ~178°. Absorption max (methanolic HCl): 540 nm.